

IN THE CLAIMS

1. (Previously presented) An implant having a tissue/implant interface, comprising an implant having an outer surface;  
a crosslinked bioactive polymer layer adjacent to at least a portion of the outer surface;  
a polyacid within the bioactive polymer layer; and  
controlled release microspheres different from the polyacid and containing a tissue response modifier within the bioactive polymer layer, wherein the controlled release microspheres provide[[s]] the tissue response modifier to the site of implantation in a quantity effective to control tissue response at the site of implantation.
2. (Withdrawn) The implant of claim 1, wherein the bioactive polymer layer is self-assembled with metal cations.
3. (Withdrawn) The implant of claim 2, wherein metal cations are  $\text{Fe}^{3+}$  or  $\text{Ca}^{2+}$ .
4. (Withdrawn) The implant of claim 2, wherein the self-assembled bioactive polymer layer is a synthetic polymer.
5. (Withdrawn) The implant of claim 2, wherein the self-assembled bioactive polymer layer is a mussel adhesive protein.
6. (Withdrawn) The implant of claim 2, wherein the self-assembled bioactive polymer layer is assembled from humic acid.
7. (Withdrawn) The implant of claim 1, wherein the bioactive polymer layer comprises glutamic acid.
8. (Original) The implant of claim 1, wherein the bioactive polymer layer further comprises covalently bound poly(ethylene oxide), phosphatidyl choline, polyvinyl alcohol, polyethylene imine, an adhesive ligand, or a combination thereof.

9. (Previously presented) The implant of claim 1, wherein the polymer in the bioactive polymer layer is a hydrogel.
10. (Original) The implant of claim 9, wherein the hydrogel is polyvinyl alcohol.
11. (Previously presented) The implant of claim 10, wherein the hydrogel further comprises acrylic acid, humic acid, nafion, or another polymeric acid, or combinations comprising at least one of the foregoing acids.
12. (Withdrawn) The implant of claim 1, wherein the implant further comprises an additional bioactive polymer layer.
13. (Withdrawn) The implant of claim 12, wherein the additional bioactive polymer layer comprises a hydrogel.
14. (Original) The implant of claim 1, wherein the bioactive polymer layer is formed by the polymerization of 2-hydroxyethyl methacrylate, a fluorinated acrylate, acrylic acid, methacrylic acid, or a combination comprising one of the foregoing monomers with an ethylenically unsaturated co-monomer.
15. (Withdrawn) The implant of claim 1, wherein the bioactive polymer layer is formed by co-polymerization of 2-hydroxyethyl methacrylate with hydroxypropyl methacrylate, N-vinyl pyrrolidinone, 2-hydroxyethyl acrylate, glycerol methacrylate, n-isopropyl acrylamide, N,N-dimethylacrylamide, glycidyl methacrylate, or a combination thereof.
16. (Withdrawn) The implant of claim 1, wherein the bioactive polymer layer is formed by co-polymerization of 2-hydroxyethyl methacrylate, N-vinyl pyrrolidinone, and 2-N-ethylperflouroctanesulfanamido ethyl acrylate in the presence of EGDMA.

17. (Original) The implant of claim 1, wherein the tissue response is inflammation, fibrosis, fibroblast formation, fibroblast function, cell proliferation, neovascularization, cell injury, cell death, leukocyte activation, leukocyte adherence, lymphocyte activation, lymphocyte adherence, macrophage activation, macrophage adherence, thrombosis, neoplasia, protein adhesion to the implant, or a combination comprising at least one of the foregoing responses.

18. (Original) The implant of claim 1, wherein the tissue response modifier comprises an anti-fibrotic agent, steroidal anti-inflammatory agent, non-steroidal anti-inflammatory agent, anti-proliferative agent, cytokine, cytokine inhibitor, growth factor, vascular growth factor, neutralizing antibody, adhesive ligand, hormone, cytotoxic agent, or a combination comprising at least one of the foregoing tissue response modifiers.

19. (Original) The implant of claim 1, comprising a tissue response modifier which affects inflammation.

20. (Withdrawn) The implant of claim 1, comprising a tissue response modifier which affects neovascularization.

21. (Withdrawn) The implant of claim 1, comprising a first tissue response modifier which affects inflammation and a second tissue response modifier which affects neovascularization.

22. (Withdrawn) The implant of claim 1, wherein the tissue response modifier comprises 2-(3-benzophenyl)propionic acid, 9- $\alpha$ -fluoro-16- $\alpha$ -methylprednisolone, methyl prednisone, fluoroxyprednisolone, 17-hydroxycorticosterone, cyclosporin, (+)-6-methoxy- $\alpha$ -methyl-2-naphthalene acetic acid, 4-isobutyl- $\alpha$ -methylphenyl acetic acid, Mitomycin C, transforming growth factor alpha, anti-transforming growth factor beta, epidermal growth factor, vascular endothelial growth factor, anti-transforming growth factor beta antibody, anti-fibroblast antibody, anti-transforming growth factor beta receptor antibody, arginine-glycine-aspartic acid, REDV, or a combination comprising at least one of the foregoing tissue response modifiers.

23. (Withdrawn) The implant of claim 1, wherein the controlled release microspheres comprise PLGA.

24. (Withdrawn) The implant of claim 1, wherein the controlled release microspheres comprise predegraded PLGA microspheres.

25. (Withdrawn) The implant of claim 1, wherein the controlled release microspheres comprise PEG-treated microspheres.

26. (Withdrawn) The implant of claim 26, wherein the controlled release microspheres comprise a mixture of standard and predegraded microspheres.

27. (Withdrawn) The implant of claim 1, wherein the controlled release microspheres further comprise PEG-treated microspheres.

28. (Withdrawn) The implant of claim 1, wherein the site of implantation is the gastrointestinal tract, biliary tract, urinary tract, genital tract, central nervous system or endocrine system.

29. (Withdrawn) The implant of claim 1, wherein the site of implantation is at blood vessels, bones, joints, tendons, nerves, muscles, the head, the neck, or organs.

30. (Previously presented) The implant of claim 38, wherein the implant is a prosthesis, an artificial organ, a repair device, an implantable drug delivery system, or a biosensor.

31. (Withdrawn) A controlled release delivery system, comprising a mixture of predegraded and untreated microspheres.

32. (Withdrawn) The controlled release delivery system of claim 31, wherein the microspheres comprise PLGA.

33. (Withdrawn) The controlled release delivery system of claim 31, wherein predegraded microspheres are made by stirring standard microspheres in a solvent for a time sufficient to produce a rough surface of the microsphere.

34. (Withdrawn) The controlled release delivery system of claim 31, further comprising PEG-treated microspheres.

35. (Withdrawn) The controlled release delivery system of claim 31, wherein the tissue response modifier comprises an anti-fibrotic agent, steroidal anti-inflammatory agent, non-steroidal anti-inflammatory agent, anti-proliferative agent, cytokine, cytokine inhibitor, growth factor, vascular growth factor, neutralizing antibody, adhesive ligand, hormone, cytotoxic agent, or a combination comprising at least one of the foregoing tissue response modifiers.

36. (Withdrawn) The controlled release delivery system of claim 31, wherein the tissue response modifier comprises 2-(3-benzophenyl)propionic acid, 9- $\alpha$ -fluoro-16- $\alpha$ -methylprednisolone, methyl prednisone, fluoroxyprednisolone, 17-hydroxycorticosterone, cyclosporin, (+)-6-methoxy- $\alpha$ -methyl-2-naphthalene acetic acid, 4-isobutyl- $\alpha$ -methylphenyl acetic acid, Mitomycin C, transforming growth factor  $\alpha$ , anti-transforming growth factor  $\beta$ , epidermal growth factor, vascular endothelial growth factor, anti-transforming growth factor  $\beta$  antibody, anti-fibroblast antibody, anti-transforming growth factor  $\beta$  receptor antibody, arginine-glycine-aspartic acid, REDV, or a combination comprising at least one of the foregoing tissue response modifiers.

37. (Withdrawn) A tissue/implant interface comprising the controlled release delivery system of claim 31.

38. (Previously presented) The implant of claim 1, wherein the implant is a device.

39. (Previously presented) An implant having a tissue/implant interface, comprising an implant having an outer surface;  
a crosslinked bioactive, controlled release polymer layer adjacent to at least a portion of the outer surface, and comprising a first tissue response modifier covalently bound to or entrapped within the polymer layer;  
a polyacid within the bioactive, controlled release polymer layer; and  
controlled release microspheres different from the polyacid and containing a second tissue response modifier within the bioactive, controlled release polymer layer, wherein the controlled release microspheres provide the second tissue response modifier to the site of implantation in a quantity effective to control tissue response at the site of implantation.

40. (Previously presented) The implant of claim 39, wherein the polymer of the bioactive polymer layer is a hydrogel.

41. (Previously presented) The implant of claim 39, wherein the bioactive, controlled release polymer layer is formed by the polymerization of 2-hydroxyethyl methacrylate, a fluorinated acrylate, acrylic acid, methacrylic acid, or a combination comprising one of the foregoing monomers with an ethylenically unsaturated co-monomer.

42. (Previously presented) The implant of claim 39, wherein the implant is a device.

43. (Previously presented) The implant of claim 42, wherein the device is a prosthesis, an artificial organ, a repair device, an implantable drug delivery system, or a biosensor.

44. (Previously presented) An implant having a tissue/implant interface, comprising an implant having an outer surface;  
a crosslinked bioactive, controlled release polymer layer adjacent to at least a portion of the outer surface that regulates the diffusion rate of small molecules;  
a polyacid within the bioactive polymer layer; and  
controlled release microspheres different from the polyacid and containing a tissue response modifier within the bioactive polymer layer, wherein the controlled release microspheres provide the tissue response modifier to the site of implantation in a quantity effective to control tissue response at the site of implantation.

45. (Previously presented) The implant of claim 44, wherein the polymer of the bioactive polymer layer is a hydrogel.

46. (Previously presented) The implant of claim 44, wherein the bioactive, controlled release polymer layer is formed by the polymerization of 2-hydroxyethyl methacrylate, a fluorinated acrylate, acrylic acid, methacrylic acid, or a combination comprising one of the foregoing monomers with an ethylenically unsaturated co-monomer.

47. (Previously presented) The implant of claim 44, wherein the implant is a device.

48. (Previously presented) The implant of claim 47, wherein the device is a prosthesis, an artificial organ, a repair device, an implantable drug delivery system, or a biosensor.

49. (Previously presented) The implant of claim 1, wherein the polyacid comprises acrylic acid, humic acid, nafion, or another polymeric acid, or combinations comprising at least one of the foregoing acids.

50. (Previously presented) The implant of claim 1, wherein the polyacid comprises a humic acid.

51. (Previously presented) The implant of claim 1, wherein the polymer of the bioactive polymer layer is a polyvinyl alcohol, and wherein the polyacid comprises a humic acid.

52. (Previously presented) The implant of claim 1, wherein the controlled release microspheres comprise poly(lactic acid), poly(glycolic acid), poly(lactic-glycolic acid), or combinations comprising at least one of the foregoing.

53. (Previously presented) The implant of claim 39, wherein the polyacid comprises acrylic acid, humic acid, nafion, or another polymeric acid, or combinations comprising at least one of the foregoing acids.

54. (Previously presented) The implant of claim 39, wherein the controlled release microspheres comprise poly(lactic acid), poly(glycolic acid), poly(lactic-glycolic acid), or combinations comprising at least one of the foregoing.

55. (Previously presented) The implant of claim 39, wherein the controlled release microspheres comprise poly(lactic-glycolic acid) microspheres.

56. (Previously presented) The implant of claim 39, wherein the controlled release microspheres comprise predegraded poly(lactic-glycolic acid) microspheres.

57. (Previously presented) The implant of claim 39, wherein the controlled release microspheres comprise a mixture of standard and predegraded microspheres.

58. (Previously presented) The implant of claim 57, wherein the controlled release microspheres comprise poly(lactic-glycolic acid) microspheres.

59. (Previously presented) The implant of claim 39, wherein the controlled release microspheres comprise PEG-treated microspheres.



60. (Previously presented) The implant of claim 44, wherein the polyacid comprises acrylic acid, humic acid, nafion, or another polymeric acid, or combinations comprising at least one of the foregoing acids.

61. (Previously presented) The implant of claim 44, wherein the controlled release microspheres comprise poly(lactic acid), poly(glycolic acid), poly(lactic-glycolic acid), or combinations comprising at least one of the foregoing.

62. (Previously presented) The implant of claim 44, wherein the controlled release microspheres comprise poly(lactic-glycolic acid) microspheres.

63. (Previously presented) The implant of claim 44, wherein the controlled release microspheres comprise predegraded poly(lactic-glycolic acid) microspheres.

64. (Previously presented) The implant of claim 44, wherein the controlled release microspheres comprise a mixture of standard and predegraded microspheres.

65. (Previously presented) The implant of claim 64, wherein the controlled release microspheres comprise poly(lactic-glycolic acid) microspheres.

66. (Previously presented) The implant of claim 44, wherein the controlled release microspheres comprise PEG-treated microspheres.